



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>4</sup> :</b> C07D 401/14, 405/14, 409/14	<b>A1</b>	<b>(11) International Publication Number:</b> WO 87/ 00171 <b>(43) International Publication Date:</b> 15 January 1987 (15.01.87)
<b>(21) International Application Number:</b> PCT/DK86/00076 <b>(22) International Filing Date:</b> 26 June 1986 (26.06.86) <b>(31) Priority Application Number:</b> 2883/85 <b>(32) Priority Date:</b> 26 June 1985 (26.06.85) <b>(33) Priority Country:</b> DK  <b>(71) Applicant (for all designated States except US):</b> NOVO INDUSTRI A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> GRØNVALD, Frederik, Christian [DK/DK]; 19, Dronningeengen, DK-2950 Vedbæk (DK). BRÆSTRUP, Claus [DK/ DK]; 78, Frederiksborgvej, DK-4000 Roskilde (DK).  <b>(74) Agent:</b> LEHMANN & REE; 26, Frederiksberg Allé, DK-1820 Frederiksberg C. (DK).		<b>(81) Designated States:</b> AT (European patent), AU, BE (Eu- ropean patent), CH (European patent), DE (Euro- pean patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> AMINO ACID DERIVATIVES  <b>(57) Abstract</b>  1-Aminobut-3-en derivatives having optionally substituted furanyl, thienyl, pyridyl and/or pyrrolyl in the 4-position and 3-carboxypiperidin-1-yl, 3-carboxytetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl in the 1-position potentiate GABA'ergic neurotransmission.		

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## AMINO ACID DERIVATIVES.

Summary of the invention

The present invention relates to novel N-(butenyl substituted) azaheterocyclic carboxylic acids of the general formula I



wherein  $\text{R}^1$  and  $\text{R}^2$  are the same or different and each represents furanyl, thienyl, pyridyl or pyrrolyl each of which may be substituted one, two or three times by halogen or lower alkyl, and  $\text{R}^3$  represents 3-carboxypiperidin-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or salts thereof.

15 Background of the invention

In the last decade, intensive pharmacological research concerning  $\gamma$ -aminobutyric acid (hereinafter designated GABA), a neurotransmitter in the central nervous system, has taken place.

20 Increased GABA'ergic activity is useful in the treatment of anxiety, epilepsy and muscular and movement disorders. Furthermore, these compounds can be used as sedatives.

In U.S. patent specification No. 4,383,999 (Smithkline Beckmann Corporation) some derivatives of N-(4-phenylbuten-3-yl)azaheterocyclic carboxylic acids which have, furthermore, inter alia, phenyl, 4-fluorophenyl, cyclohexyl or thienyl in the 4-position, are described. It is stated therein that the compounds are useful as inhibitors of GABA uptake.

30 According to J.Pharm.Exp.Therap., 228 (1984), 109 et seq., N-(4,4-diphenyl-3-butenyl)nipecotic acid (designated SK&F 89976A), N-(4,4-diphenyl-3-butenyl)guvacine (designated SK&F 100330A), N-(4,4-diphenyl-3-butenyl)- $\beta$ -homoproline

(designated SK&F 100561) and N-(4-phenyl-4-(2-thienyl)-3-butenyl)nipecotic acid (designated SK&F 100604J) are active inhibitors of GABA uptake.

Detailed practice of this invention

5           It has now been found that novel compounds of the general formula I stated in Claim 1 below exhibit GABA uptake inhibitory properties and exert useful pharmacological effects on the central nervous system, i.e., a selective enhancement of GABA activity. Surprisingly, these  
10 effects are superior to those of previously known compounds. Compounds of formula I may be used for treatment of, for example, pain, anxiety, epilepsy, certain muscular and movement disorders, other neurological disorders and as sedatives and hypnotics.

15           Herein furanyl is 2-furanyl or 3-furanyl, thienyl is 2-thienyl or 3-thienyl, pyridyl is 2-pyridyl, 3-pyridyl or 4-pyridyl and pyrrolyl is 2-pyrrolyl or 3-pyrrolyl. Furthermore, halogen is, preferably, chloro, bromo and fluoro. The lower alkyl group contains less than 8 carbon  
20 atoms, preferably less than 5 carbon atoms, and some especially preferred alkyl groups are methyl and ethyl. Examples of preferred substituents  $R^1$  and  $R^2$  are 3-methylthienyl, 4-methylthienyl and N-methylpyrrolyl.

Compounds of formula I are, for example: .

25 N-(4,4-di(furan-2-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(furan-3-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(thien-3-yl)but-3-enyl)nipecotic acid,  
N-(4-(5-chlorothien-2-yl)-4-(thien-2-yl)but-3-enyl)nipecotic  
30 acid,  
N-(4,4-di(pyrid-3-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(5-methylpyrrol-2-yl)but-3-enyl)nipecotic acid,  
N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)nipecotic acid,  
N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)nipecotic acid,  
35 N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)nipecotic acid,  
N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(furan-2-yl)but-3-enyl)guvacine,

- N-(4,4-di(furan-3-yl)but-3-enyl)guvacine,  
N-(4,4-di(thien-2-yl)but-3-enyl)guvacine,  
N-(4,4-di(thien-3-yl)but-3-enyl)guvacine,  
N-(4,4-di(pyrid-4-yl)but-3-enyl)guvacine,  
5 N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)guvacine,  
N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)guvacine,  
N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)guvacine,  
N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)guvacine,  
N-(4,4-di(furan-2-yl)but-3-enyl)- $\beta$ -homoproline,  
10 N-(4,4-di(furan-3-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4,4-di(thien-2-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4,4-di(thien-3-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4-(furan-2-yl)-4-(thien-2-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4-(furan-3-yl)-4-(thien-3-yl)but-3-enyl)- $\beta$ -homoproline,  
15 N-(4-(furan-2-yl)-4-(thien-3-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4-(furan-3-yl)-4-(thien-2-yl)but-3-enyl)- $\beta$ -homoproline,  
N-(4,4-di(3-methylthien-2-yl)but-3-enyl)guvacine,  
N-(4,4-di(3-methylthien-2-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(3-methylthien-2-yl)but-3-enyl)- $\beta$ -homoproline,  
20 N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl)-  
guvacine,  
N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl)-  
nipecotic acid,  
N-(4-(3-methylthien-2-yl)-4-(thien-2-yl))but-3-enyl)- $\beta$ -  
25 homoproline,  
N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl)-  
guvacine,  
N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl)-  
nipecotic acid,  
30 N-(4-(N-methyl-pyrrol-2-yl)-4-(thien-2-yl))but-3-enyl)- $\beta$ -  
homoproline,  
N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)guvacine,  
N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)nipecotic acid,  
N-(4,4-di(N-methyl-pyrrol-2-yl)but-3-enyl)- $\beta$ -homoproline,  
35 N-(4-(3-bromo-thien-2-yl)-4-(thien-2-yl))but-3-enyl)-  
nipecotic acid,  
and salts thereof.

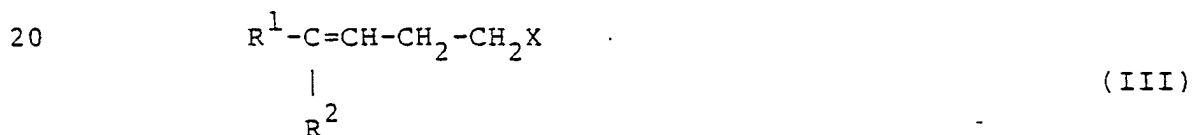
Compounds of formula I may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or  
5 fractional crystallisation.

One embodiment of this invention is non-toxic pharmaceutically acceptable salts of compounds of formula I. Salts include those derived from inorganic or organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric,  
10 acetic, lactic, maleic and phthalic acid. Furthermore, salts include salts of the carboxylic acid group, for example sodium, potassium, calcium and magnesium salts and salts with a strong base such as triethylamine.

Compounds of formula I may be prepared by N-alkyla-  
15 tion of a compound of the general formula II

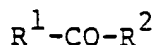


wherein  $\text{R}^3$  has the same meaning as the above  $\text{R}^3$  with the proviso that the carboxy group is protected (for example, as an ester group), with a compound of the general formula III



wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined in Claim 1, and X represents halogen. This reaction may be carried out in an inert solvent  
25 in the presence of an alkali metal carbonate, for example, potassium carbonate, for example, at reflux temperature or lower temperature, for from about 8 to 24 hours. The solvent may conveniently be an alcohol, acetone or N,N-dimethylformamide. Thereafter, compounds of formula I may be  
30 prepared by hydrolysis of the resulting ester, for example by refluxing a mixture of an aqueous sodium hydroxide solution and an alcohol such as methanol or ethanol for from about 1 to 4 hours.

Compounds of formula III may be prepared by reacting the corresponding disubstituted ketones of the general formula V



(V)

5 wherein  $R^1$  and  $R^2$  each is as defined above, with a Grignard reagent, i.e., cyclopropyl magnesium bromide, followed by ring opening and dehydration of the intermediate carbinol derivative by treatment with hydrogen bromide in acetic acid.

Compounds of formula I are useful because they  
10 possess pharmacological activity in man. In particular, the compounds of formula I are useful as inhibitors of GABA uptake.

For the above indications, the dosage will vary depending on the compound of formula I employed, on the mode  
15 of administration and on the therapy desired. However, in general, satisfactory results are obtained with a dosage of from about 15 mg to about 2 g of compounds of formula I, conveniently given from 1 to 5 times daily, optionally in sustained release form. Usually, dosage forms suitable for  
20 oral administration comprise from about 25 mg to about 1 g of the compounds of formula I admixed with a pharmaceutical carrier or diluent. No toxic effects have been observed at these levels.

The compounds of formula I may be administered in  
25 pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit approximately the same order of activity as the free base forms.

This invention also relates to pharmaceutical compositions comprising a compound of formula I or a  
30 pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutical carrier or diluent. The compositions of this invention may be prepared by conventional techniques to appear in conventional forms, for example, capsules or tablets.

The pharmaceutical carrier employed may be conventional solid or liquid carriers. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

10 If a solid carrier for oral administration is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, usually, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may appear in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension.

The pharmaceutical compositions of this invention can be made following the conventional techniques of the pharmaceutical industry involving mixing, granulating and compressing or variously mixing and dissolving the ingredients as appropriate to give the desired end product.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired place, such as orally or parenterally, the oral route being preferred.

Any novel feature or combination of features described herein is considered essential.

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which, however are not to be construed as limiting. The examples illustrate some preferred embodiments.

#### Example 1

35 a) To a suspension of 1.3 g of magnesium in 20 ml of anhydrous tetrahydrofuran, 8.0 g of cyclopropyl bromide in 15 ml of anhydrous tetrahydrofuran was added under nitrogen.



The reaction mixture was kept under reflux for 1 hour and then cooled to ambient temperature. To the reaction mixture, 5.4 g of di(thien-2-yl)ketone dissolved in 15 ml of anhydrous tetrahydrofuran was added dropwise. After refluxing for 30 minutes, the reaction mixture was chilled and 35 ml of a concentrated ammonium chloride solution was carefully added. To the resulting mixture, 50 ml of water was added and the suspension was extracted twice with 50 ml of ether. The ether extracts were washed with water, dried and evaporated leaving 10 7.6 g of an oil.

The crude product was dissolved in 60 ml of acetic acid and a mixture of 30 ml of acetic acid and 15 ml of 48% hydrobromic acid was added at 5°C. The mixture was stirred for 30 minutes and then poured into 300 ml of water. The 15 resulting emulsion was extracted twice with 100 ml of ether. The ether extracts were washed with water, dried and evaporated leaving 8.5 g of an oil.

From this oil, 5.2 g of 4,4-di(thien-2-yl)but-3-enyl bromide having a boiling point (hereinafter b.p.) of 20 137°C (0.05 mm Hg) was obtained by fractional distillation in vacuum.

b) A suspension of 5.0 g of 4,4-di(thien-2-yl)but-3-enyl bromide, 3.4 g of nipecotic acid ethyl ester and 3.3 g of potassium carbonate in 150 ml of dry acetone was kept 25 under reflux for 15 hours. The reaction mixture was evaporated and, after addition of 30 ml of water, the resulting solution was extracted twice with 50 ml of ethyl acetate. The ethyl acetate extracts were dried and evaporated leaving 7.3 g of an oil. By column chromatography on silica 30 gel using methanol as eluent, N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid ethyl ester was isolated.

5.3 g of this compound was dissolved in 100 ml of ethanol and 200 ml of an 8 N sodium hydroxide solution was added. The mixture was heated at reflux for 1 hour, cooled 35 and acidified by adding 10% hydrochloric acid. The resulting solution was evaporated and 100 ml of water was added to the residue. The resulting acid solution was extracted with ethyl acetate and the dried extract was evaporated to give N-(4,4-

di(thien-2-yl)buten-3-yl)nipecotic acid which after crystallization from ethyl acetate had a melting point (hereinafter m.p.) of 62 - 64°C (decomposition).

#### Example 2

5 A solution of 34 ml of n-butyllithium in 30 ml of anhydrous ether was cooled to -65°C under nitrogen and 5.3 ml of 3-bromothiophen in 10 ml anhydrous ether was added dropwise over a period of 10 min. The reaction mixture was stirred at -65°C for 1 hour and 2.7 ml of ethyl 4-bromo-  
10 butyrate in 10 ml of anhydrous ether was added slowly. The reaction was stirred for 4 hours while the temperature raised to -20°C. 20 ml water was added and the mixture was stirred for 5 minutes after which the aqueous layer was removed. The ether layer was washed with 20 ml of water and the combined  
15 aqueous phases were extracted with 50 ml of ether. The combined organic phases were dried over anhydrous sodium sulfate which after evaporation yielded 9 g of 1-bromo-4,4-di(3-methylthien-2-yl)but-3-en as an oil. This compound was without further purification used for coupling with ethyl  
20 nipecolate following the procedure according to b) in Example 1 whereby N-(4,4-di(3-methylthien-2-yl)but-3-en)nipecotic acid hydrochloride was obtained.

$R_f = 0.38$  (MeOH; silicagel)

#### Examples 3 - 11

25 The compounds of formula I stated in table I, below, were prepared analogously to the method described in Example 1 (method A) and Example 2 (method B).

Table I

Exam- ple	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	m.p. °C
3	4-methylthien-2-yl	4-methylthien-2-yl	nipecotic acid	60-63
4	5-methylthien-2-yl	5-methylthien-2-yl	nipecotic acid	72-76
5	3-methylthien-2-yl	5-methylthien-2-yl	nipecotic acid	57-60
6	3-methylthien-2-yl	5-methylthien-2-yl	guvacine	40-42
7	thien-2-yl	3-methylthien-2-yl	nipecotic acid	86-88
8	thien-2-yl	3-methylthien-2-yl	guvacine	84-88
9	N-methylpyrrol-2-yl	N-methylpyrrol-2-yl	nipecotic acid	44
10	5-chloro-4-methylthien-2-yl	5-chloro-4-methylthien-2-yl	nipecotic acid	78-82
11	thien-2-yl	3-methylthien-2-yl	β-homoproline	oil

In Examples 5 through 8 and 11, Method A was used and in the remaining examples, Method B was used. The compounds prepared were hydrochlorides (HCl).

Example 12Preparation of Capsules.

<u>Ingredients</u>	<u>Mg per Capsule</u>
N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid	125
5 Magnesium stearate	2
Lactose	200

The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1 - 10 5 times daily to enhance GABA'ergic activity in the central nervous system.

Example 13Preparation of Tablets.

<u>Ingredients</u>	<u>Mg per Tablet</u>
15 N-(4,4-di(thien-2-yl)but-3-enyl)nipecotic acid	200
Corn starch	46
Polyvinyl pyrrolidone	12
Magnesium stearate	1

The compound is thoroughly mixed with two thirds of 20 the corn starch and granulated. The granules obtained are dried, mixed with the remaining ingredients and compressed into tablets.

The capsules or tablets thus prepared are administered orally. Similarly, other compounds of formula I 25 can be used.

Pharmacological test

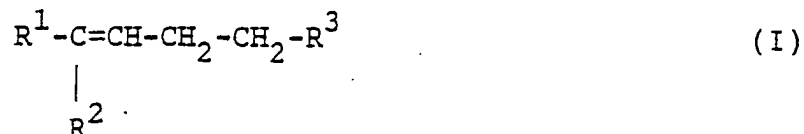
GABA-uptake was measured essentially as described by Fjalland (Acta Pharmacol. et. toxicol. (1978), 42, 73 - 76) using 25 mM of 3H-GABA as substrate. The results obtained 5 appears from the following table.

<u>Compound</u>	<u>IC<sub>50</sub> (nM)</u>
SKF 100330 A	380
<u>N</u> -(4,4-di(3-methylthien-2-yl)buten-3-yl)- nipecotic acid, HCl	90
10 <u>N</u> -(4-(thien-2-yl)-4-(3-methylthien-2-yl)- buten-3-yl)- $\beta$ -homoproline, HCl	70
<u>N</u> -(4,4-di( <u>N</u> -methylpyrrol-2-yl)buten-3-yl)- nipecotic acid, HCl	60
15 <u>N</u> -(4-(thien-2-yl)-4-(3-methylthien-2-yl)- buten-3-yl)nipecotic acid, HCl	110

The obtained values are means from 2 separate experiments using 3 - 5 different concentrations of test compound.

C l a i m s

1. 1-Aminobut-3-en derivatives of formula I



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wherein  $\text{R}^1$  and  $\text{R}^2$  are the same or different and each represents furanyl, thienyl, pyridyl or pyrrolyl each of which may be substituted one, two or three times by halogen or lower alkyl, and  $\text{R}^3$  represents 3-carboxypiperidin-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or salts thereof.

10

2. Derivatives according to claim 1, characterized in that the substituents are chloro or methyl.

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3. Derivatives according to claim 1 or 2, wherein  $\text{R}^1$  and  $\text{R}^2$  each is thienyl optionally substituted by lower alkyl.

20

4. Derivatives as prepared in any of the above examples.

5. Pharmaceutical compositions containing a compound of formula I stated in any one of the preceding claims.

25

6. Compositions according to claim 5, characterized in that they contain from about 25 mg to about 1 g of the compound.

7. A process for preparing compounds of formula I stated in claim 1 or a salt thereof, characterized in hydrolysing a compound of the general formula IV

30



35

wherein  $\text{R}^1$  and  $\text{R}^2$  each are as defined above and  $\text{R}'^3$  has the same meaning as the above  $\text{R}^3$  with the proviso that the carboxy group is protected, and, if desired, converting

a compound of formula I into a salt thereof or converting a salt into a compound of formula I.

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# INTERNATIONAL SEARCH REPORT

International Application No. PCT/DK86/00076

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) <sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC . 4

C 07 D 401/14, 405/14, 409/14

## II. FIELDS SEARCHED

Minimum Documentation Searched <sup>7</sup>

Classification System	Classification Symbols
IPC 1	C 07 d 99/04, /06
IPC 2,3,4	C 07 D 401/14, 405/14, 409/14
Nat Cl	12p: 1/01, 2

.../...

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>

SE, NO, DK, FI classes as above

## III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	US, A, 4 383 999 (SMITHKLINE BECKMAN CORPORATION) 17 May 1983 see inter alia claim 1,21 and example 18 & EP, 0066456 JP, 57203063 AU, 84003/82 AU, 552050	1,5,7
X	US, A, 4 514 414 (SMITHKLINE BECKMAN CORPORATION) 30 April 1985 see inter alia claim 1, 6 and example 12	1,5,7

<sup>10</sup> Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

1986-09-24

Date of Mailing of this International Search Report

1986 -09- 26

International Searching Authority

Swedish Patent Office

Signature of Authorized Officer

*Lennart Elfving*  
Lennart Elfving



## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II

Fields Searched (cont)

US Cl 424: 266, 267;  
514: 422;  
542: 400, 429;  
546: 283, 284;  
548: 527

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
  
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
  
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.  
☐ No protest accompanied the payment of additional search fees.